

# Recent advances in functional nanostructures as cancer photothermal therapy

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**Abstract:** Being a non-invasive and relatively safe technique, photothermal therapy has attracted a lot of interest in the cancer treatment field. Recently, nanostructure technology has entered the forefront of cancer therapy owing to its ability to absorb near-infrared radiation as well as efficient light to heat conversion. In this study, key nanostructures for cancer therapy including gold nanoparticles, magnetite iron oxide nanoparticles, organic nanomaterials, and novel two-dimensional nanoagents such as MXenes are discussed. Furthermore, we briefly discuss the characteristics of the nanostructures of these photothermal nanomaterial agents, while focusing on how nanostructures hold potential as cancer therapies. Finally, this review offers promising insight into new cancer therapy approaches, particularly in vivo and in vitro cancer treatments.

**Keywords:** photothermal therapy, nanostructures, near-infrared, plasmonic, cancer therapy

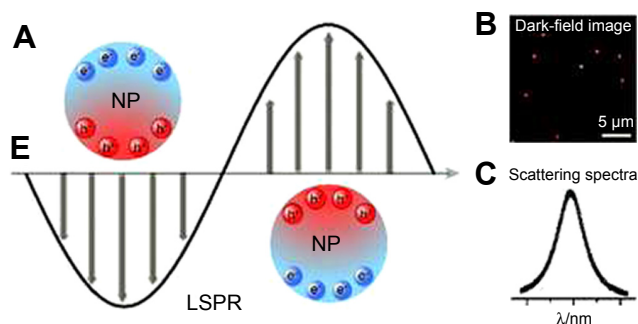
## Introduction

Globally, cancer as an invasive and malignant disease is considered the second leading cause of mortality. As per the American Cancer Society, the estimated number of cancer incidence in 2017 is 1,688,780 new cancer cases and 600,920 cancer deaths in USA, which implies a potential increase of 70% over the next 2 decades.<sup>1,2</sup> Current cancer therapies, such as surgical excision, chemotherapy, radiation therapy, or even combination therapy, have severe limitations. Surgery could result in hurt or injury in the adjacent healthy critical tissues, and both chemotherapy and radiotherapy exhibit violent side effects.<sup>3</sup>

Recently, photothermal therapy (PTT) has gained a great deal of attention due to its excellent performance in cancer treatment. PTT depends on heat generation upon exposure of tumor cells to near-infrared radiation (NIR).<sup>4-6</sup> PTT agents absorb light energy, which causes electron excitation and subsequent non-radiative relaxation. This will lead to gain kinetic energy, which in turn results in heat generation in the medium surrounding the PTT agents.<sup>7-9</sup> This PTT approach is considered as non-invasive therapy in which the induced thermal energy develops cell membrane disruption or protein denaturation of the surrounding tumor cells.<sup>10</sup>

Coupled with that, a major breakthrough in nanotechnology has been developed resulting in the production of various nanomaterials for many applications. Due to their unique optical properties, nano-scaled materials, especially noble metal nanoparticles (NPs), are promising in the nanomedicine and biomedical fields.<sup>11-14</sup> The noble metal NPs such as gold (Au) and silver (Ag) have a unique photo-physical phenomenon, called localized surface plasmon resonance (LSPR), which enhances their photo-absorption.<sup>15-18</sup> Consequently, they are considered as PTT because of their ability to stimulate hyperthermia in the cancerous cells, when exposed to NIR.<sup>19-21</sup> This phenomenon is due to the special optical properties of noble metal NPs, which are able

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**Figure 1** (A) Schematic description of localized surface plasmon resonance in metal NPs. (B) Dark-field image of NPs. (C) Scattering spectrum of a single NP.

**Notes:** Reproduced from Xie T, Jing C, Long YT. Single plasmonic nanoparticles as ultrasensitive sensors. *Analyst*. 2017;142(3):409–420.<sup>25</sup> <http://pubs.rsc.org/en/Content/ArticleLanding/2017/AN/C6AN01852A#divAbstract>, with permission of The Royal Society of Chemistry.

**Abbreviations:** LSPR, localized surface plasmon resonance; NP, nanoparticle.

to absorb the light energy in NIR region (ie, 650–900 nm). Then, the absorbed light energy is converted to heat leading to tumor cell damage and tumor tissue necrosis.<sup>3</sup>

To illustrate, the surface plasmon resonance (SRP) effect means that the metal-free electrons that exist in the conduction band oscillate around the particle surface when exposed to the electromagnetic field of light. Subsequently, this oscillation leads to charge separation and formation of dipole oscillation (Figure 1). At a certain frequency, the oscillation will reach its maximum which is known as SPR, which supports the light absorption of the NPs, especially the noble metals (ie, Au and Ag).<sup>22–25</sup>

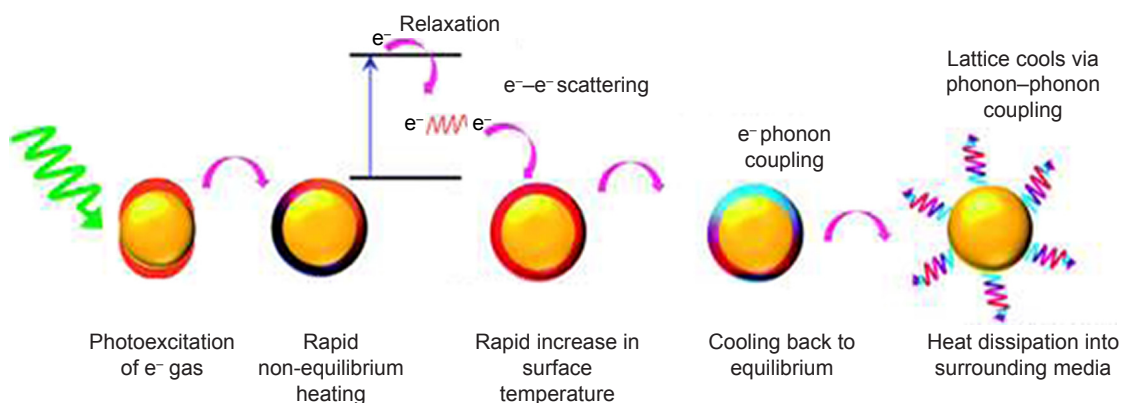
The conversion of the absorbed light to heat proceeds through three main photo-physical processes. The first and second processes allow for the formation of a hot metallic lattice in the metal NPs, and the last one allows for a cooling off, which means heat dissipation from the NPs to the surrounding

environment. Accordingly, the dissipated energy will heat up the cancerous cells around the Au nanoparticles (AuNPs) causing cell destruction. However, such energy conversion and dissipation occur when the frequency of the incident light is overlapped with the SPR absorption band.<sup>24–27</sup> Figure 2 shows the schematic presentation of the three processes included in the light to heat conversion mechanism.

On the other hand, exposure of the healthy cells to electromagnetic radiation of light raises the concern about the safety of this type of therapy. With respect to the LSPR frequency, the incident laser light is generally in the visible region or in the NIR region. In vivo, the radiation can be normally absorbed in the tissue by water, hemoglobin, and melanin.<sup>3</sup> However, NIR laser light is weakly absorbed by these absorbents; hence, it can penetrate the skin without causing damage to normal tissues.<sup>24,28</sup> Under such circumstances, many researchers have opened the door for the application of several nanomaterials, which strongly absorb the NIR and, as a result of SPR effect, generate sufficient heat to cause tumor cell death.

## Functional nanostructures as cancer PTT

In this study, we introduce a recent literature review about nanomaterials used as a cancer PTT over the past 5 years. Different nanostructures developed even from the same material or combination of two or three PTT agents were reported to enhance the efficiency or to decrease the toxicity. For simplicity, this review covers mainly the application of diverse nano-scaled materials, either single or hybrid nanostructures, but does not cover the implication of any therapeutic agent or anticancer drug of the nanomaterials.



**Figure 2** Schematic illustration of light to heat conversion by plasmonic nanostructures.

**Notes:** Step 1 is excitation of metal nanoparticles by the absorbed light photons, which results in particle oscillation and charge separation. Step 2 is conversion of the absorbed light to heat through electron–electron relaxation and electron–phonon relaxation processes, which result in the formation of hot metallic lattice. Step 3 is cooling off the metal structure through electron–phonon coupling and phonon–phonon relaxation, which cause heat dissipation. Reproduced from Webb JA, Bardhan R. Emerging advances in nanomedicine with engineered gold nanostructures. *Nanoscale*. 2014;6(5):2502.<sup>27</sup> <http://pubs.rsc.org/en/content/articlelanding/2014/nr/c3nr05112a#divAbstract>, with permission of The Royal Society of Chemistry.

## Au-based nanomaterials

One of the most promising PTT nanomaterials for cancer treatment is Au nanostructures, as they can be synthesized in different forms such as nanorods, nanoshells, nanocages, or nanospheres. Beyond their plasmonic effect, they have an enhanced permeability to tumor vasculature, resulting in higher retention in tumor tissue. Because the tumor vascular system possesses gaps ranging in size from 100 nm to 2  $\mu$ m, AuNPs can penetrate easily; these NPs are retained due to lymphatic clearance deficiency in the cancerous cells.<sup>18</sup> Although AuNPs can successfully pass into the tumor tissue, they are subjected to phagocytosis by macrophages. Hence, AuNPs are sometimes coated with biocompatible polymers to inhibit reuptake by phagocytic cells.<sup>29</sup> In addition, AuNPs were reported as good biocompatible NPs with low cytotoxicity.<sup>30</sup> Nanomaterials are unable to differentiate between cancerous cells and normal cells. In some studies, however, AuNPs were conjugated with a specific antibody-targeted cancer receptor to achieve minimal binding with healthy tissues.<sup>31–33</sup>

The optical properties of different Au nanostructures are greatly affected by altering their shapes and sizes. Research studies used these properties to tune the resonance in the NIR region according to the desired applications.<sup>27</sup> In detail, more complex shapes such as Au nanorods (AuNRs), nanoshells, and nanostars exhibited more enhanced LSPR effect than simple AuNPs.<sup>34,35</sup> Kelly et al<sup>36</sup> demonstrated that complex geometrical shapes improved the polarizability of Au nanostructures due to additional bumps and protrusions. To illustrate, polarizability of AuNPs arises from their diameter only, while polarizability of Au-nanostar was enhanced by their projections, which increase the overall polarizability resulting in red shift in the plasmon resonance wavelength.<sup>37</sup> In addition to shape, increasing the size of Au nanostructures enhances the electron oscillation around Au nanostructure leading to increasing the oscillation time and decreasing the frequency. This phenomenon is called phase retardation, which results in prolonged lifetime of plasmon and red shift of the resonance wavelength as well.<sup>27,38</sup>

Findings from recent research support the application of Au-based nanomaterials as PTT. Ali et al<sup>39</sup> studied the effect of AuNRs on human oral squamous cell carcinoma (HSC-3) by analyzing the data from Raman spectroscopy, metabolomics, and proteomics mass spectrometry. They claimed that the AuNR-treated cancer cells exhibited high levels of phenylalanine resulting in cell apoptosis. Similarly, a long-term in vivo study was carried out in mouse tumor tissues to discover the efficiency of AuNRs as PTT agents.<sup>40</sup> The authors compared the apoptotic effect induced by gold nanorods conjugated to

rifampicin (AuNRs@RF) to the apoptotic effect induced by gold nanorods conjugated to polyethylene glycole (AuNRs@PEG). By using proteomics analysis, it was found that AuNRs@RF has more efficient endocytosis and easier cellular uptake resulting in increased neutrophil cell death (NETosis).

Moreover, AuNRs were found to minimize metastasis via inhibition of cancer cell migration.<sup>41</sup> This occurs because AuNR surface, when conjugated to specific peptides, induces changes in migration-related proteins (integrins), which result in controlling cancer metastasis. Another key point is the effect of Au nanomaterial concentration on NIR-induced hyperthermia. Singh et al<sup>42</sup> investigated the optimal concentration of AuNRs to be an efficient PTT in vitro using human esophagogastric tissues. They studied different concentrations of AuNRs and variable power densities. Their results showed a linear relationship between temperature elevation and laser power and AuNR concentration.

During treatment with a PTT agent, excessive reactive oxygen species (ROS) could be produced as a result of heat shock.<sup>43–45</sup> Thus, ROS can cause protein damage leading to cell death. Sometimes, ROS levels increased in degenerative diseases such as Alzheimer or even in progressive disease such as cancer.<sup>46–49</sup> Interestingly, platinum-coated Au nanorods were proved to be used in cancer therapy as a PTT with simultaneous ROS scavenging.<sup>50</sup> Platinum shells of varying thickness were examined and showed no interference with the photothermal effect of AuNRs, as well as no impairment of the thermal response to NIR laser waves.

In addition, a new strategy was reported by Wu et al<sup>51</sup> to synthesize nanotubes of Au-attapulgitite composite, where attapulgitite is a natural and biocompatible clay. The nanocomposite was prepared by the assembly of AuNPs on the surface of attapulgitite. The authors stated that the synthesized tube-like nanocomposite could act as an efficient PTT when tested using A549 cells (human adenocarcinoma cell). Furthermore, a new Au nanostructure (Au nanobipyramids) was reported to be applied for breast cancer detection and treatment in which Au nano-bipyramids were bio-conjugated with 2-naphthalenethiol and folic acid to target and kill human breast (adenocarcinoma) cells.<sup>52</sup> The authors revealed that the conjugated Au nano-bipyramids are capable of quantitative detection of the MCF-7 cells as well as enhancement of photothermal effect in vivo and in vitro.

On the contrary, there are some challenges in the clinical application of Au nanostructures as PTT agents. For instance, lack of stability inside the body and agglomeration of Au nanostructures is the most challenging factor upon in vivo application.<sup>27</sup> Some modifications, such as attaching a

surface ligand and dispersion in phosphate buffer with suitable pH, could be carried out during synthesis to increase the in vivo stability and decrease the aggregation, respectively.<sup>53</sup> However, the use of natural surface ligands results in lower yield from Au nanostructures,<sup>54</sup> and the use of high salt or basic buffer can cause surface instability and aggregation of the nanostructures.<sup>55</sup>

## Iron oxide ( $\text{Fe}_3\text{O}_4$ ) NPs

Due to unique magnetism, non-toxicity, biodegradability, and biocompatibility, magnetite  $\text{Fe}_3\text{O}_4$  NPs have been widely reported in biomedical applications.<sup>56-61</sup> For instance,  $\text{Fe}_3\text{O}_4$  NPs were extensively used in drug delivery systems, cell targeting, and in magnetic resonance imaging (MRI) as contrast agents. In addition, they possess a unique surface, which is able to carry targeting molecules for cancer cells and go deeply into tumor tissues.<sup>62</sup> Furthermore,  $\text{Fe}_3\text{O}_4$  NPs have been proved useful for cancer treatment due to their magnetic hyperthermia in which induced high temperatures were achieved and controlled by alternating magnetic field (AFM).<sup>63</sup> The generated heat is sufficient to destroy cancerous cells but may affect healthy tissues. For this reason, the use of NIR laser radiation (widely used in therapy and diagnosis) to induce hyperthermia has an added safety advantage compared to AFM.<sup>64</sup>

$\text{Fe}_3\text{O}_4$  nanomaterials of different shapes (ie, spherical, hexagonal, and wire-like particles) were investigated for photothermal effect on human esophageal cancer cells (Eca-109). It was found that NIR-induced hyperthermia by spherical  $\text{Fe}_3\text{O}_4$  NPs exhibited significant cytotoxicity and suppression of tumor growth.<sup>64</sup> Shen et al<sup>65</sup> have synthesized both individual and clustered  $\text{Fe}_3\text{O}_4$  NPs and investigated their thermo-therapeutic effect in vivo and in vitro. They used human lung adenocarcinoma epithelial (A549) cells for in vitro testing and flow cytometry analysis to investigate the cell apoptosis effect. The clustered  $\text{Fe}_3\text{O}_4$  NPs were shown to have higher NIR-induced hyperthermia and increased cell death compared to individual one.

The effect of coating  $\text{Fe}_3\text{O}_4$  NPs with an anti-biofouling polymer was studied and compared to commercial magnetic NPs (FeREX, BioPAL) for their anticancer activity.<sup>66</sup> The study showed that highly crystallized iron oxide nanoparticles (HCIONPs) offered more potential photothermal effect in vivo and in vitro due to their preferred lattice orientations. Consequently, this approach was suggested for clinical use in cancer treatment. Furthermore, Zhou et al<sup>67</sup> developed iron/iron oxide core-shell nanoparticles ( $\text{Fe}@\text{Fe}_3\text{O}_4$  NPs) that have advantages of NIR photothermal therapeutic effect, selective magnetic targeting, and MRI for complete tumor treatment. Another study investigated the efficiency of FePt NPs functionalized

with folates to target breast cancer cells EMT-6.<sup>68</sup> The findings revealed that the FePt NP exhibited intracellular explosions accompanied by rupture of cancerous cell membranes.

The main limitation of most studies is the use of highly intense laser irradiation, which might exceed the safe limit for cutaneous tissues ( $0.33 \text{ W/cm}^2$ ). However, Espinosa et al<sup>69</sup> mitigated this drawback and reported the dual magnetic and photothermal activity of  $\text{Fe}_3\text{O}_4$  nanocubes. The authors applied a magnetic field in alternating patterns and NIR laser of reasonable irradiation density ( $0.3 \text{ W/cm}^2$ ). Such dual approach showed complete cell death and tumor ablation even at low iron doses.

## Organic nanomaterials

Owing to their enhanced biocompatibility and low toxicity, organic nanomaterials have recently been reported for a wide variety of biomedical applications.<sup>70</sup> In particular, they can be used as PTT agents because they exhibit an efficient light-to-heat conversion. Moreover, organic materials have a strong NIR absorption resulting from their diffused bi-electrons.<sup>71</sup> Therefore, reduced graphene oxide (rGO) nanosheets as an example have a high extension coefficient ( $3.6 \text{ L g}^{-1} \text{ cm}^{-1}$ ).<sup>72</sup> Carbon-based nanomaterials (ie, carbon nanotubes and graphene), organic dyes, and polymer nanocarriers are the most widely reported organic-based photothermal nanoagents.

Liang et al<sup>73</sup> have synthesized PEGylated single-walled carbon nanotubes (SWCNTs) and demonstrated their efficiency as a PTT. They investigated the therapeutic effect of PEGylated SWCNTs on metastasis of primary 4T1 murine breast tumor to lymph node. The findings showed the ability of PEGylated SWCNTs to suppress the primary tumor and the pulmonary metastasis. Similarly, a novel SWCNT-peptide composite showed an effective photothermal effect on colon 26 and HepG2 cells after 3 minutes of NIR radiation.<sup>74</sup>

Graphene, as a carbon-based nanomaterial, has biomedical applications such as biosensors, drug carriers, and a very recent application as a PTT due to its strong NIR absorption.<sup>75-77</sup> However, graphene is still considered to exhibit some biological toxicity because of poor dispersibility in physiological fluids. Consequently, most of the graphene-based PTT agents were modified with surface functionalization to mitigate the bio-toxicity limitation.<sup>77-79</sup> To figure out photothermal efficiency of graphene and graphene oxide (GO), their ability to produce heat after laser irradiation was investigated and compared to AuNRs using an integrating sphere method and the time constant method.<sup>80</sup>

Graphene or GO as two-dimensional (2D) nanosheets with large surface area can be mixed with certain functional NPs for diagnostic and therapeutic purposes.<sup>81</sup> For example,



BaGdF<sub>5</sub> NPs attached to the PEG-coated GO surface were fabricated by Zhang et al<sup>82</sup> for both MRI and photothermal cancer therapy. The synthesized nanocomposites were injected into mice bearing HeLa tumor and irradiated for 10 minutes with 808 nm laser (power density of 0.5 W/cm<sup>2</sup>). When the tumor tissue samples were collected for histological examination, the results showed that the treated group acquired thermonecrosis and cell shrinkage. Chen et al<sup>83</sup> developed radiolabeled reduced GO coated with PEG (<sup>131</sup>I-rGO-PEG) for combined radiotherapy and PTT. The results showed high synergistic effect on 4T1 murine breast cancer therapy due to the combination between radioactive <sup>131</sup>I and strong NIR absorption of PEG-coated rGO as well as no apparent animal toxicity.

The literature revealed many articles concerned with the use of organic dyes such as cyanine and porphyrin derivatives as efficient photothermal agents. The most common cyanine derivative indocyanine green (ICG) dye, which was approved by the US Food and Drug Administration for clinical use, was reported in combination with nanocarriers as a PTT with a good efficiency *in vitro* and *in vivo* for tumor ablation.<sup>84–86</sup> The nanocarriers containing ICG dye showed enhanced aqueous stability and better cellular uptake compared to the direct dyes. However, most of these studies have poor photostability at high-power laser irradiation, which means limited use to preclinical studies.<sup>70</sup> Similarly, porphyrin-based nanomaterials showed its activity as PTT for the treatment of different tumors as well as their biodegradability and biocompatibility.<sup>87</sup> However, it is important to mention that porphyrin nanoagents exhibit short absorption wavelength (600–700 nm), which restricts their *in vivo* application.<sup>70</sup>

In the last decade, NPs of conductive polymers have been reported for biomedical applications due to their high stability and biocompatibility. In particular, polypyrrole (PPy) and poly-(3,4-ethylenedioxythiophene):poly(4-styrenesulfonate) (PEDOT:PSS) have strong NIR absorbance, making them suitable as photothermal agents for cancer therapy. Both PPy and PEDOT:PSS were examined for tumor ablation *in vivo* and *in vitro*, showing high efficiency without undesired effects.<sup>88–91</sup> However, the clinical use of polymer NPs is still limited due to lack of safety data.<sup>70</sup>

## Combined nanomaterials

In general, the combination between two PTT agents to synthesize nanocomposites or core-shell NPs provides novel physical and chemical properties.<sup>92</sup> In addition, these nanocomposites act as multi-function nanomaterials with tunable size and composition. The optical properties were enhanced while using two or more nanostructures to synthesize a hybrid PTT.<sup>93</sup> Therefore, strong plasmonic effect and

surface-enhanced Raman scattering were reported for many combined PTT.

Hybrid NPs consisting of Au and Fe<sub>3</sub>O<sub>4</sub> were synthesized to get new and unique physical and chemical properties. The plasmonic effect was investigated by using optical absorption measurements such as UV-vis<sup>92</sup> and surface-enhanced Raman spectra.<sup>93</sup> Owing to their potential application as PTT, the optical properties of Fe<sub>3</sub>O<sub>4</sub>@Au core-shell were simulated by using the extended Mie theory.<sup>94–96</sup> Investigations of absorption cross-section spectra as well as the relationship between the resonance wavelength and the elevated temperature were conducted.<sup>97</sup> In addition, Ahmed et al<sup>98</sup> studied the *in vitro* cell viability of Fe<sub>3</sub>O<sub>4</sub>@AuNPs by using the MTT assay. They found 50 µg/mL of Fe<sub>3</sub>O<sub>4</sub>@AuNPs to be non-toxic and biocompatible.

Another example of hybrid therapy is the combination between ICG organic dye and Fe<sub>3</sub>O<sub>4</sub> NPs investigated by Niu et al.<sup>99</sup> The authors used the two synergistic PTT agents encapsulated in perfluoropentane-based polylactide-co-glycolide (Fe<sub>3</sub>O<sub>4</sub>/ICG@PLGA/PFP NPs) and evaluated their efficiency toward tumor ablation. When Fe<sub>3</sub>O<sub>4</sub>/ICG@PLGA/PFP NPs were incubated with MCF-7 human breast cancer cells and irradiated with 808 nm laser for 5 minutes, they showed tissue deformation and significant cell death. Furthermore, effectiveness of this dual NIR therapy was assessed *in vivo* by using mice bearing MCF-7 cells. The results revealed reduced tumor size and inhibition of tumor growth with no significant toxicity in vital organs such as liver, kidney, heart, spleen, and brain.

Meng et al<sup>100</sup> developed golden SWCNT hybrids with enhanced NIR absorption, excellent water dispersibility, and better biocompatibility. The novel hybrids were synthesized by layer-by-layer self-assembly of two different polysaccharides on the SWCNT skeleton, followed by growing AuNPs on the surface. Highly effective photothermal activity was achieved, when the golden SWCNTs were incubated overnight with HeLa cells and irradiated for 15 minutes with 808 nm laser diode.

In addition, graphene-based hybrid PTT has been recently reported to have the advantages of carbon-based materials and metal NPs. For example, combination of GO with AuNPs revealed an enhanced tumor ablation *in vivo* and *in vitro* at lower laser irradiation (0.75 W/cm<sup>2</sup>).<sup>101</sup> Similarly, reduced GO/AuPd NPs/PEG-coated nanocomposites were evaluated for the suppression of HeLa cells *in vitro* showing good results after laser irradiation for 10 minutes.<sup>102</sup> For the purpose of improving light-to-heat conversion as well as targeting the tumor tissues, combined GO/magnetic iron NP hybrids were also reported in the literature.<sup>81,103</sup> However,

laser-induced hyperthermia in these articles were substituted by magnetic hyperthermia, which is induced by AFM to mitigate the limited penetration of NIR into the tissues.<sup>104</sup>

Nanocomposites of AuNRs coated with pyrrole conductive polymer have gained a great interest due to high photostability and biocompatibility in addition to improved photothermal activity.<sup>105</sup> Likewise, Au/pyrrole NPs with Fe<sub>3</sub>O<sub>4</sub> NPs deposited on the surface were synthesized by Feng et al<sup>106</sup> for cancer therapy. The Au/pyrrole@Fe<sub>3</sub>O<sub>4</sub> nanocomposites were considered to be multifunctional nanoagents with enhanced photothermal conversion, superparamagnetic properties, and good biocompatibility.

## Novel 2D materials

New family of 2D nanosheets have been recently reported in the literature for many biomedical applications. Owing to high biocompatibility, excellent physicochemical performance as well as unique photothermal conversion efficiency, various 2D nanostructures are considered to be promising PTT agents for cancer therapy.<sup>107</sup> MXenes are recently reported but widely spread new 2D materials, having a general formula of M<sub>n+1</sub>X<sub>n</sub>, where M represents a transition metal and X represents carbon or nitrogen.<sup>108,109</sup> One of the most powerful 2D PTT nanoagents is Ti<sub>3</sub>C<sub>2</sub> (MXene), which shows strong NIR absorption and high light-to-heat conversion property. To explain,

the exfoliated ultrathin MXene nanosheets demonstrate semimetal-like band energy structure; consequently, they have the LSPR effect similar to metal NPs.<sup>110</sup> The same condition is applied for the transition of metal dichalcogenides such as tungsten sulfide (WS<sub>2</sub>), molybdenum sulfide (MoS<sub>2</sub>), and titanium sulfide (TiS<sub>2</sub>) as well as black phosphorus.<sup>111,112</sup>

Lin et al<sup>110</sup> synthesized phospholipid-stabilized ultrathin Ti<sub>3</sub>C<sub>2</sub> nanosheets (MXene) by prolonged etching of Ti<sub>3</sub>AlC<sub>2</sub> using hydrofluoric acid (HF), followed by intercalation with tetrapropylammonium hydroxide (TPAOH) and surface modification with soybean phospholipids (SP). They evaluated the cytotoxicity of Ti<sub>3</sub>C<sub>2</sub>-SP nanoflakes and the tumor ablation ability in vivo and in vitro by using 4T1 tumor-bearing mice and murine 4T1 breast cancer cells, respectively. The results showed that the groups treated with the stabilized MXenes revealed high percentage of 4T1 cancer cell death in vitro and significant decrease of tumor size in vivo after exposure to NIR laser irradiation for few minutes. Similarly, by using the same mouse model, MXene-based hybrids such as MnO<sub>x</sub>-Ti<sub>3</sub>C<sub>2</sub> composites were prepared and investigated for tumor ablation and MRI by Dai et al.<sup>113</sup>

Table 1 summarizes different nano-scaled PTT agents applied for different types of cancer cells. From Table 1, it is clearly observed that the combination between two or more PTT agents contributed in reducing the power densities of

**Table 1** Summary of different nanomaterials reported as PTT agents applied on various types of tumor cells

PTT nanoagent	Cancer cell type	Photothermal conditions	References
<b>Au-based nanomaterials</b>			
AuNRs	Human oral squamous cell carcinoma (HSC-3)	808 nm NIR laser irradiation (5.8 W/cm <sup>2</sup> ) for 3 min	41
Au-attapulgit composite	Human lung adenocarcinoma cells (A549)	808 nm laser (0.5 W/cm <sup>2</sup> ) for 15 min	51
AuNBPs	Human breast cancer cells (MCF-7)	808 nm laser (2 W/cm <sup>2</sup> ) for 5 min	52
<b>Magnetic Fe<sub>3</sub>O<sub>4</sub> nanomaterials</b>			
Fe <sub>3</sub> O <sub>4</sub> NPs	A549 cells	808 NIR (5 W/cm <sup>2</sup> ) for 1–3 min	65
Fe <sub>3</sub> O <sub>4</sub> nanocubes	Three malignant cell lines (SKOV3, PC3, and A431)	Dual magneto-photothermal (alternating magnetic field and NIR laser [0.3 W/cm <sup>2</sup> for 5 min])	69
<b>Organic nanomaterials</b>			
SWCNT composite	The murine rectum carcinoma cell line (colon 26) and human hepatocellular carcinoma cell line (HepG2)	808 nm NIR laser (1.2 W/cm <sup>2</sup> ) for 3 min	74
GO-BaGdF <sub>5</sub> nanocomposites	Mice bearing HeLa tumor cells	808 nm laser (0.5 W/cm <sup>2</sup> ) for 10 min	82
Polypyrrole hollow microspheres	Human umbilical vein endothelial cells (HUVECs)	808 nm laser (6 W/cm <sup>2</sup> ) for 5 min	90
<b>Combination therapy</b>			
Fe <sub>3</sub> O <sub>4</sub> /ICG@PLGA/PFP NPs	MCF-7	808 nm laser for 5 min	99
GO/AuNPs	Squamous cell carcinoma (SSC7)	808 nm laser (0.3 W/cm <sup>2</sup> ) for 10 min	101
AuPd NPs-rGO nanocomposites	HeLa cells	808 nm laser (1 W/cm <sup>2</sup> ) for 10 min	102
<b>Novel 2D materials</b>			
Ti <sub>3</sub> C <sub>2</sub> nanosheets (MXenes)	Murine 4T1 breast cancer cells	808 nm laser (1 W/cm <sup>2</sup> ) for 5 min	110
<b>Others</b>			
Antimony NPs	4T1 cells	808 nm laser (2 W/cm <sup>2</sup> ) for 5 min	114
Iron carbide (Fe <sub>5</sub> C <sub>2</sub> ) NPs	Human ovarian cancer cell line (SK-OV-3)	808 nm laser (0.8 W/cm <sup>2</sup> ) for 5 min	115
Tungsten oxide nanorods	HeLa cells	980 nm laser (0.35 W/cm <sup>2</sup> ) for 8 min	116

**Abbreviations:** AuNRs, gold nanorods; AuNBPs, gold nanopyramids; GO, graphene oxide; NIR, near-infrared; NP, nanoparticle; PTT, photothermal therapy; SWCNT, single-walled carbon nanotube.

laser irradiation near to the safety limit in addition to decreasing the exposure radiation time.

## Conclusion and future perspective

Throughout this review, new insights for cancer treatment have been addressed, focusing on the promising benefits of employing the PTT types. It is evident from ineffective conventional treatments that there is a desperate necessity for distinct and unique treatments. As extensively explained, nanostructure technology has the potential to play critical functions in cancer therapy, through directly acting as PTT. Of note, nanostructures with various shapes were revealed as PTT due to their strong NIR absorption and efficient light-to-heat conversion. Investigation through various nanostructure studies revealed that the mentioned concepts attempt to strengthen their overall photothermal therapeutic behavior. As represented by numerous reports, therapies including AuNPs, Fe<sub>3</sub>O<sub>4</sub> NPs, organic nanomaterials, and novel 2D nanoagents have the potential to directly enhance the in vivo and in vitro cancer therapies. In addition, hybrid nanomaterials with two or more PTT agents have superior advantages of synergism, which leads to enhanced efficiency and reduced toxicological effects of every single therapy. To sum up, nanostructures are considered promising candidates for tumor ablation as PTT agents due to their unique optical properties. However, in vivo stability and more detailed toxicity studies should be covered in the future for the PTT nanoagents to be clinically approved.

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## Disclosure

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